510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

K190109

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of eravacycline at concentrations 0.016 – 32 µg/mL to the MicroScan Dried Gram-Negative MIC/Combo Panels for susceptibility testing of non-fastidious Gram-negative organisms.

C. Measurand:

Eravacycline in the dilution range of 0.016 – 32 µg/mL.

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST)

E. Applicant:

Beckman Coulter, Inc.

F. Proprietary and Established Names:

MicroScan Dried Gram-Negative MIC/Combo Panels with Eravacycline (ERV) (0.016 – 32 µg/mL)

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product code:

   JWY, Manual, Antimicrobial Susceptibility Test Systems

LTT, Panels, Test, Susceptibility, Antimicrobial

LRG, Instrument for Auto Reader and Interpretation of Overnight Susceptibility Systems

LTW, Susceptibility Test Cards

4. Panel:

   83- Microbiology

H. Intended Use:

1. Intended use(s):

   For use with MicroScan Dried Gram Negative MIC/Combo Panels and Dried Gram Negative Breakpoint Combo panels. MicroScan panels are designed for use in determining antimicrobial agent susceptibility and/or identification to the species level of aerobic and facultatively anaerobic gram-negative bacilli.

2. Indication(s) for Use

   The MicroScan Dried Gram-Negative MIC/Combo Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram-negative bacilli. After inoculation, panels are incubated for 16-20 hours at 35 °C ± 1°C in a non-CO_2 incubator, and read either visually or with MicroScan instrumentation, according to the Package Insert.

   This particular submission is for the addition of the antimicrobial eravacycline (ERV) at concentrations of 0.016 – 32 µg/mL to the test panel.

   The gram-negative organisms which may be used for eravacycline susceptibility testing on this panel are as follows:

   Eravacycline has been shown to be active both clinically and *in vitro* against the gram-negative bacteria listed below according to the FDA drug approved label:
   Citrobacter freundii
   Enterobacter cloacae
   Escherichia coli
   Klebsiella oxytoca
   Klebsiella pneumoniae

   Eravacycline has been shown to be active *in vitro* only against the gram negative bacteria listed below according to the FDA drug approved label:
   Citrobacter koseri
   Klebsiella (Enterobacter) *aerogenes*

3. Special conditions for use statement(s):

   For Prescription use only.

   The following limitations are included in labeling:

   > *Due to the lack of an intermediate interpretive category for Eravacycline, results obtained with C. freundii, E. cloacae, K. oxytoca and K. pneumoniae with both the Prompt and turbidity inoculation methods and read using autoSCAN-4 and manual read showed potential very major errors compared to the reference method. If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results when the Eravacycline MIC is 0.5 for C. freundii complex, E. cloacae complex, K. oxytoca and K. pneumoniae.*
   >
   > *Results obtained with C. freundii and eravacycline with turbidity inoculation and the Prompt inoculation system with the autoSCAN-4 read were outside of essential agreement compared to the reference method. Results should be confirmed using a manual read.*
   >
   > *The ability of the MicroScan Dried Gram-Negative Panels to detect non-susceptible isolates to Eravacycline is unknown for C. koseri, E. coli, E. (K.) aerogenes and K. oxytoca because an insufficient number of non-susceptible strains were available at the time of comparative testing.*

4. Special instrument requirements:

   MicroScan panels can be read either manually or automatically on the WalkAway or autoSCAN-4 instrument systems.

I. Device Description:

The MicroScan Dried Gram-Negative MIC/Combo panel with eravacycline is used to determine the quantitative and/or qualitative antimicrobial agent susceptibility of aerobic and facultatively anaerobic gram negative bacilli colonies grown on solid media. After inoculation, panels are incubated for 16-20 hours at 35°C ± 1°C in a non-CO_2 incubator and read either visually or with MicroScan instrumentation according to the package insert.

Inoculation methods: Turbidity, Prompt Inoculation System

Read methods: Manual, MicroScan WalkAway System and MicroScan autoSCAN-4

J. Substantial Equivalence Information:

1. Predicate device name(s):
   MicroScan Dried Gram-Negative MIC/Combo Panels – Ceftazidime/Avibactam

2. Predicate 510(k) number(s):
   K172337

3. Comparison with predicate:

Table 1. Comparison with the Predicate Device

Similarities		
Item	**Device K190109**	**Predicate K172337**
Device	MicroScan Dried Gram Negative MIC/Combo Panels - Eravacycline	MicroScan Dried Gram Negative MIC/Combo Panels – Ceftazidime/Avibactam
Intended Use	For use with MicroScan Dried Gram Negative MIC/Combo Panels and Dried Gram Negative Breakpoint Combo panels. MicroScan panels are designed for use in determining antimicrobial agent susceptibility and/or identification to the species level of aerobic and facultatively anaerobic gram-negative bacilli.	Same
Technology	Overnight microdilution MIC Susceptibility Test	Same
Specimen	Isolated colonies from cultures	Same
Inoculation Method	Turbidity and Prompt	Same
Incubation Temperature	35 °C ± 1°C	Same
Incubation Atmosphere	Aerobic	Same
Incubation Time	16-20 hours	Same
Reading Method	Automated (WalkAway or autoSCAN-4) or Manual	Same
Result Reported	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (SIR)	Same

Differences		
Item	**Device**	**Predicate**
Antimicrobial Agent	Eravacycline (0.016-32 µg/mL)	Ceftazidime/Avibactam (0.25/4 – 64/4 µg/mL)

K. Standard/Guidance Document Referenced (if applicable):

1. Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA
2. CLSI M07-A11. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 11th ed. (January, 2018)
3. CLSI M100. Performance Standards for Antimicrobial Susceptibility Testing. 28th ed. (January 2018)

L. Test Principle:

The antimicrobial susceptibility tests are dehydrated miniaturizations of the broth dilution susceptibility test. Various antimicrobial agents are diluted in Mueller Hinton broth supplemented with calcium and magnesium to concentrations spanning the range of clinical interest. Breakpoint Combo panels use concentrations equivalent to the categorical breakpoints of FDA and/or CLSI. After inoculation and rehydration with a standardized suspension of organism and incubation at 35°C for a minimum of 16 hours, the minimum inhibitory concentration (MIC) for the test organism is determined by observing the lowest antimicrobial concentration showing inhibition of growth.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study was conducted at three external sites using 11 isolates of gram negative bacilli that were consistent with the intended use. The range of Eravacycline dilutions tested was 0.016 – 32 µg/mL. Isolates were tested in triplicate over three days for a total of 297 data points. The isolates tested in the reproducibility study included *C. freundii* (one isolate) *K. aerogenes* (one isolate), *E. cloacae* (two isolates), *E. coli* (three isolates), *K. oxytoca* (one isolate) and *K. pneumoniae* (three isolates).

Inocula were prepared using both the turbidity and Prompt method and results were read manually and with the WalkAway and autoSCAN-4 instrument systems. All data points were on-scale and the majority were within ± one doubling dilution agreement as compared to the mode MIC (Table 2). Because all results were on-scale, only a single value is reported for each read method.

Table 2. Reproducibility of Eravacycline with all Inoculation and Read Methods.

Read Method	Prompt Inoculation	Turbidity Inoculation
WalkAway	294/297 (99.0%)	294/297 (99.0%)
autoSCAN-4	294/297 (99.0%)	293/297 (98.7%)
Manual	294/297 (99.0%)	292/297 (98.3%)

The reproducibility results were acceptable.

b. Linearity/assay reportable range:

N/A

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Inoculum Density Check. A spectrophotometric device, the MicroScan Turbidity Meter, was used to ensure quality control of the turbidity inoculum method. The inocula prepared using the turbidity method inocula were standardized using the MicroScan Turbidity Meter with a reading of 0.08 ± 0.02 (equivalent to a 0.5 McFarland barium sulfate turbidity standard). The digital reading was recorded each day of use.

During the clinical study, organism suspension density data was collected using the QC strain *E. coli* ATCC 25922 for suspensions inoculated using both the Prompt and turbidity inoculation methods. For the turbidity method, the average colony count was 4.9 X 10^5 CFU/mL, within the expected range of 2-8 X 10^5 CFU/mL. For suspensions inoculated using the Prompt method, the average colony counts were slightly higher than the expected range at 9.1 X 10^5 CFU/mL.

Organism density data was also collected for suspensions prepared using the Prompt inoculum preparation method for organisms included in the reproducibility study. Colony counts were within the acceptable range for *E. coli* (nine suspensions), *K. oxytoca* (three suspensions) and *K. pneumoniae* (nine suspensions). Colony counts were elevated for *C. freundii* (1.0 X 10^6, three suspensions), *E. cloacae* (1.1 X 10^6, six suspensions) and *K. aerogenes* (1.4 X 10^6, three suspensions). Although the inoculum concentration was higher than the expected range, the essential agreement (EA) for *E. cloacae* and *K. aerogenes* was acceptable for all read methods. The EA for *C. freundii* was acceptable for both the WalkAway and manual read methods; a low EA for *C. freundii* with Prompt inoculation and the autoSCAN-4 read method (with MIC values lower than the reference method) is addressed in a labeling limitation (see Comparison Studies below).

Purity Check. Purity check plates were performed for all isolates tested.

Growth Failure Rate. During the course of the study there were no growth failures with the MicroScan panel with eravacycline.

Quality Control Testing. The CLSI recommended QC organisms (*E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853) were tested using all inoculation and read methods using twelve concentrations of eravacycline (0.016 – 32 µg/mL). The reference panel was inoculated using the turbidity method only. Results of QC testing are shown in Table 3 below.

Although not indicated for clinical use with eravacycline, *P. aeruginosa* ATCC 27853 provided MIC results that are within-range for both the Prompt and turbidity inoculation methods with all read methods (WalkAway, autoSCAN-4 and manual read). For *E. coli* ATCC 25922, quality control results were within the acceptable range of both the Prompt and turbidity inoculation method with the WalkAway and manual read methods. However, results obtained with the autoSCAN-4 read method were within the acceptable range for only 85% (103/121) and 86.0% (104/121) of trials using the Prompt and turbidity inoculation method, respectively. The out of range QC results were not due to technical error. The sponsor included the following footnote to the quality control table in the device labeling:

QC testing with E. coli ATCC 25922 may provide out-of-range results using autoSCAN-4, results should be confirmed using a manual read.

In addition, to indicate to users that *P. aeruginosa* ATCC 27853 should be used only for the purpose of QC, the sponsor included the following footnote to the quality control table in the device labeling:

Organism intended for quality control testing only

Table 3. Quality Control Results for Eravacycline

Organism	Conc. (µg/mL)	Reference[a]	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
E. coli ATCC 25922 Expected Range 0.03 – 0.12 µg/mL	≤0.016				18			17
	0.03	119	121	121	103	121	101	104
	0.06	2					19	
	0.12							
	0.25							
	0.5							
	1							
	2							
	4							
	8							
	16							
	≥32							

Organism	Conc. (µg/mL)	Reference[a]	Prompt Inoculation Method			Turbidity Inoculation Method		
			Manual	WalkAway	AS4	Manual	WalkAway	AS4
P. aeruginosa ATCC 27853[b]	≤0.016							
	0.03							
	0.06							
	0.12							
	0.25							
	0.5							
	1							
Expected Range 2 - 16 µg/mL	2		1			8		12
	4	89	120	117	121	112	119	109
	8	32		3		1	2	
	16							
	≥32							

[a] Reference panel was inoculated using the turbidity method only and read manually.
[b] *P. aeruginosa* is not an indicated organism for eravacycline

d. Detection limit:

N/A

e. Analytical specificity:

N/A

f. Assay cut-off:

N/A

2. Comparison studies:

a. Method comparison with predicate device:

The results obtained with the MicroScan Dried Gram-Negative MIC/Combo Panel with eravacycline (dilution range of 0.016 – 32 µg/mL) were compared to results obtained using a frozen broth microdilution reference panel (dilution range of 0.016 – 32 µg/mL) at three testing sites in the U.S.

The reference panel was prepared according to CLSI M07, 11th edition guidelines except for the use of Pluronic-F in the inoculum water for the reference panel. A validation study was performed to demonstrate equivalence between reference panels inoculated with organisms suspended in water supplemented with Pluronic-F and reference panels inoculated with autoclaved distilled water without Pluronic-F. The effect of Pluronic-F in the reference panel was determined with the following species: *C. freundii* (one isolate), *E. cloacae (*two isolates), *E. coli* (three isolates), *K. aerogenes* (one isolate), *K. oxytoca* (one isolate) and *K. pneumoniae* (three isolates). The essential agreement (EA) and categorical agreement of MIC values obtained

using Pluronic-F as the diluent as compared to MIC values obtained using autoclaved distilled water as the diluent was 100%.

For each organism tested, MicroScan panels and reference panels were inoculated using the same standardized suspension further diluted into 25 mL of water with either Pluronic-D (for the MicroScan dried panels) or Pluronic-F (for the frozen reference panels). Reference panels were inoculated using the turbidity inoculation method. MicroScan panels were inoculated using both the Prompt System and by the turbidity method and read using the WalkAway and autoSCAN-4 instruments and by manual read. The reference panels were read manually

Clinical Study:
To determine the performance of the MicroScan Dried Gram-Negative MIC/Combo Panel with eravacycline, a total of 414 *Enterobacteriaceae* clinical isolates were evaluated. The testing included the following indicated species: *C. freundii* (44 isolates), *C. koseri* (57 isolates), *E. cloacae* (20 isolates), *E. cloacae* complex (45 isolates), *E. coli* (64 isolates), *K.* (Enterobacter) *aerogenes* (55 isolates), *K. oxytoca* (49 isolates) and *K. pneumoniae* (59 isolates). An additional 21 isolates of non-indicated species were also evaluated. Of the clinical isolates, 277 (66.9%) were fresh isolates (tested within seven days of isolation), 87 (21.0%) were recent isolates (tested within one year of isolation) and 50 (12.1%) were stock isolates (tested within three years of isolation).

Challenge Study:

A total of 79 *Enterobacteriaceae* challenge isolates were evaluated. These included *C. freundii* (8 isolates), *C. koseri* (6 isolates), *E. cloacae* (16 isolates), *E. coli* (15 isolates), *K.* (Enterobacter) *aerogenes* (4 isolates), *K. oxytoca* (6 isolates) and *K. pneumoniae* (24 isolates).

For the *Enterobacteriaceae* the overall essential agreement, essential agreement of evaluable and category agreement for all inoculation and read methods was acceptable at ≥ 90% for the dilution series of 0.016 – 32 µg/m. Performance data is shown in Tables 4 and 5.

Table 4. Performance of MicroScan Dried Gram-Negative Panels with Eravacycline with *Enterobacteriaceae*, Prompt Inoculation Method, All Read Methods

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	No. S	min*	maj	vmj
WalkAway													
Clinical	414	400	96.6	412	398	96.6	410	99.0	11	403	NA	3	1
Challenge	79	77	97.5	79	77	97.5	75	94.9	33	46	NA	4	0
Combined	493	477	96.8	491	475	96.7	485	98.4	44	449	NA	7	1
autoSCAN-4													
Clinical	414	383	92.5	411	380	92.5	409	98.8	11	403	NA	3	2
Challenge	79	72	91.1	78	71	91.0	74	93.7	33	46	NA	2	3
Combined	493	455	92.3	489	451	92.2	483	98.0	44	449	NA	5	5
Manual													
Clinical	414	399	96.4	412	397	96.4	410	99.0	11	403	NA	3	1
Challenge	79	79	100.0	79	79	100.0	74	93.7	33	46	NA	3	2
Combined	493	478	97.0	491	476	96.9	484	98.2	44	449	NA	6	3

* NA, Not applicable due to only a susceptible interpretive criterion for eravacycline

EA – Essential Agreement (± 1 dilution)
CA – Category Agreement
EVAL – Evaluable isolates
NS – Non-Susceptible isolates

min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the MicroScan Dried Gram-Negative MIC/Combo Panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the MicroScan Dried Gram-Negative MIC/Combo Panel. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation provided by the MicroScan Dried Gram-Negative MIC/Combo Panel.

Table 5. Performance of MicroScan Dried Gram-Negative Panels with Eravacycline with *Enterobacteriaceae*, Turbidity Inoculation Method, All Read Methods

	Tot	No. EA	EA %	Eval EA Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	No. S	min*	maj	vmj
WalkAway													
Clinical	414	405	97.8	413	404	97.8	412	99.5	11	403	NA	1	1
Challenge	79	78	98.7	79	78	98.7	72	91.1	33	46	NA	5	2
Combined	493	483	98.0	492	482	98.0	484	98.2	44	449	NA	6	3
autoSCAN-4													
Clinical	414	396	95.7	412	394	95.6	413	99.8	11	403	NA	0	1
Challenge	79	78	98.7	79	78	98.7	72	91.1	33	46	NA	2	5
Combined	493	474	96.1	491	472	96.1	485	98.4	44	449	NA	2	6
Manual													
Clinical	414	409	98.8	413	408	98.8	413	99.8	11	403	NA	0	1
Challenge	79	79	100.0	79	79	100.0	74	93.7	33	46	NA	2	3
Combined	493	488	99.0	492	487	99.0	487	98.8	44	449	NA	2	4

* NA, Not applicable due to only a susceptible interpretive criterion for eravacycline

Due to the lack of an intermediate or resistant interpretive category for eravacycline, only major and very major errors could be determined and a number of those errors were observed. However, many of those errors were otherwise within essential agreement of the reference method. The error rates are reported as determined in the clinical study. However, the error rates are adjusted by taking into consideration the essential agreement with the reference method of MIC values resulting in the errors. The original and adjusted error rates are shown in Table 6.

The sponsor included the following footnote to the performance table in the device labeling:

> *The overall potential very major error rate for eravacycline was elevated for Enterobacteriaceae with Prompt/autoSCAN-4 and Prompt/manual read and for Turbidity inoculation with all read methods. All potential very major errors were one dilution apart from the reference method and as such fall within essential agreement. Based on the essential agreement and lack of an intermediate breakpoint for Eravacycline, the adjusted very major error rate for Enterobacteriaceae is 0%. The overall major error rate for Enterobacteriaceae was acceptable. However, potential major errors were observed for E. cloacae and K. oxytoca with Prompt/all read methods and for C. freundii and K. pneumoniae with turbidity/WalkAway. The adjusted major error rate was acceptable.*

In addition, the sponsor included the following limitation to the performance table in the device labeling related to the potential for major and very major errors:

> *Due to the lack of an intermediate interpretive category for Eravacycline, results obtained with C. freundii, E. cloacae, K. oxytoca and K. pneumoniae with both the Prompt and turbidity inoculation methods and read using autoSCAN-4 and manual read showed potential very major errors compared to the reference method. If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results when the Eravacycline MIC is 0.5 for C. freundii complex, E. cloacae complex, K. oxytoca and K. pneumoniae.*

Table 6. Original and Adjusted Major and Very Major Error Rates for Eravacycline with all Inoculation and Read Methods.

Inoculation/Read Method	Species	No. Major Errors/Total (%)		No. Very Major Errors/Total (%)	
		Original	Adjusted	Original	Adjusted
Prompt WalkAway	*All Enterobacteriaceae*	7/449 (1.6)	2/449 (0.5)	1/44 (2.3)	0
	E. cloacae	1/23 (4.3)	0	0	-
	K. pneumoniae	0	-	1/21 (4.7)	0
	K. oxytoca	2/53 (3.8)	1/55 (1.9)	0	-
Prompt autoSCAN-4	*All Enterobacteriaceae*	5/449 (1.1)	2/449 (0.5)	5/44 (11.4)	0
	C. freundii	0	-	2/4 (50.0)	0
	E. cloacae	1/23 (4.3)	0	1/13 (7.7)	0
	K. oxytoca	2/53 (3.8)	1/53 (1.9)	1/2 (50.0)	0
	K. pneumoniae	0	-	1/21 (4.8)	0
Prompt Manual	*All Enterobacteriaceae*	6/449 (1.3)	2/449 (0.5)	3/44 (6.8)	0
	C. freundii	0	-	1/4 (25.0)	0
	E. cloacae	1/23 (4.3)	0	1/13 (7.7)	0
	K. oxytoca	2/53 (3.8)	1/53 (1.9)	0	-
	K. pneumoniae	0	-	1/21 (4.8)	0
Turbidity WalkAway	*All Enterobacteriaceae*	6/449 (1.3)	1/449 (0.2)	3/44 (6.8)	0
	C. freundii	2/48 (4.2)	0	1/4 (25.0)	0
	E. cloacae	0	-	1/13 (7.7)	0
	K. pneumoniae	3/62 (4.8)	1/62 (1.6)	1/21 (4.8)	0
Turbidity autoSCAN-4	*All Enterobacteriaceae*	2/449 (0.5)	0	6/44 (13.6)	0
	C. freundii	0	-	1/4 (25.0)	0
	E. cloacae	0	-	2/13 (15.4)	0
	K. oxytoca	0	-	1/2 (50.0)	0
	K. pneumoniae	0	-	2/21 (9.5)	0
Turbidity Manual	*All Enterobacteriaceae*	2/449 (0.5)	0	4/44 (9.0)	0
	E. cloacae	0	-	1/13 (7.7)	0
	K. oxytoca	0	-	1/2 (50.0)	0
	K. pneumoniae	0	-	2/21 (9.5)	0

Results obtained with *C. freundii* showed EA and EA of evaluable results of 80.8% and 88.5% using the autoSCAN-4 read method and inoculated using the Prompt and turbidity inoculation methods, respectively. The sponsor included the following limitation in the device labeling:

> *Results obtained with C. freundii and eravacycline with turbidity inoculation and the Prompt inoculation system with the autoSCAN-4 read were outside of essential agreement compared to the reference method. Results should be confirmed using a manual read.*

To address the lack of non-susceptible isolates evaluated in the study, the sponsor included the following limitation in the device labeling:

> *The ability of the MicroScan Dried Gram-Negative Panels to detect non-susceptible isolates to Eravacycline is unknown for C. koseri, E. coli, E. (K.) aerogenes and K. oxytoca because an insufficient number of non-susceptible strains were available at the time of comparative testing.*

Resistance mechanism Characterization

Challenge isolates of *Enterobacteriaceae* harboring various molecular mechanisms of resistance noted in the FDA drug label were tested with eravacycline. The following resistance mechanisms were evaluated: *tet(A)* and *tet(B)*.

MIC Trending

An analysis of trending was conducted using the combined clinical and challenge data for each organism group and for each inoculation and read method. This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher compared to the reference method irrespective of whether the device MIC values are on-scale or not. Results that are not clearly at least one dilution lower, at least one dilution higher or in exact agreement with the CLSI reference method are not considered in the trending analysis.

Trending results for indicated species and overall trending for indicated *Enterobacteriaceae* are shown in Table 7; results were stratified by species to determine if species-related trends were observed. Species for which the difference between the percentage of isolates with higher vs. lower readings was ≥ 30% and for which the confidence interval was determined to be statistically significant were considered to show evidence of trending. Trending that provides higher or lower MIC values compared to the reference is addressed in labeling.

A trend toward lower MIC readings was observed for *Enterobacteriaceae* using the Prompt inoculation method and read manually or using the WalkAway or autoSCAN-4 instruments (Table 7). A trend toward lower MIC readings was observed for *Enterobacteriaceae* using the turbidity inoculation method and read using the autoSCAN-4 instrument. The sponsor included the following footnote to the performance table in the device labeling:

> *Eravacycline MIC values for Enterobacteriaceae were most frequently in exact agreement with the reference method. When not in agreement, results by Turbidity/autoSCAN-4 and Prompt/autoSCAN-4, Prompt/WalkAway and Prompt/Manual tended to be one doubling dilution lower than the reference method.*

Table 7. Trending for Eravacycline with *Enterobacteriaceae* with all Inoculation and Read Methods

Inoculation/ Read Method	Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
Prompt/ WalkAway	*Enterobacteriaceae*	425	178 (41.9)	222 (52.2)	25 (5.9)	-36.0 (-41.1 to -30.7)	Yes
Prompt/ autoSCAN-4	*Enterobacteriaceae*	424	271 (63.9)	143 (33.7)	10 (2.4)	-61.6 (-66.1 to -56.5)	Yes
Prompt/ Manual	*Enterobacteriaceae*	425	171 (40.2)	236 (55.5)	18 (4.2)	-36.0 (-41.0 to -30.9)	Yes
Turbidity/ WalkAway	*Enterobacteriaceae*	426	96 (22.5)	271 (63.6)	59 (13.9)	-8.69	No
Turbidity/ autoSCAN-4	*Enterobacteriaceae*	426	190 (44.6)	217 (50.9)	19 (4.5)	-40.1 (-45.2 to -34.9)	Yes
Turbidity/ Manual	*Enterobacteriaceae*	426	128 (30.1)	274 (64.3)	24 (5.6)	-24.4	No

b. Matrix comparison:

N/A

3. Clinical studies:

a. Clinical Sensitivity:

N/A

b. Clinical specificity:

N/A

c. Other clinical supportive data:

N/A

4. Clinical cut-off**:**

N/A

4. Expected values/Reference range:

Table 8. FDA Recognized Interpretive Criteria for Eravacycline

Organism	Interpretive Criteria for Eravacycline MIC (µg/mL)[a]		
	S	I	R
Enterobacteriaceae	**≤ 0.5**	**-**	**-**

[a] FDA STIC Webpage https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

N. Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device when evaluated with the current FDA-recognized eravacycline breakpoints.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a finding of substantial equivalence.

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission included a breakpoint change protocol that was reviewed and accepted by FDA. This protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The protocol outlined the specific procedures and acceptance criteria that Beckman Coulter intends to use to evaluate the MicroScan Dried Gram-Negative MIC/Combo Panels with Eravacycline (ERV) (0.016 – 32 µg/mL) when revised breakpoints for eravacycline are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Beckman Coulter will update the eravacycline device label to include (1) the new breakpoints, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.